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Journal of the Chinese Medical Association 78 (2015) 62–66

www.jcma-online.com

Original Article

Impact of warm ischemia time on the change of split renal function after minimally invasive partial nephrectomy in Taiwanese patients

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Received March 3, 2014; accepted April 30, 2014

Abstract

Background: Nephron-sparing surgery has become the standard treatment for T1 renal tumors. However, relevant data on the Taiwanese population are lacking, and most of the current literature uses global instead of split renal function (SRF) for postoperative renal function follow-up. We evaluated the postoperative renal function after minimally invasive partial nephrectomy in Taiwanese patients.

Methods: We retrospectively reviewed our database from April 2004 to July 2012 and enrolled patients who received laparoscopic partial nephrectomy (LPN) or robot-assisted partial nephrectomy (RPN). The estimated glomerular filtration rate (eGFR) and SRF were calculated as representatives of renal function. The preoperative and 6- and 12-month postoperative renal functions were assessed. Friedman test was used to evaluate pre- and postoperative renal function changes; Wilcoxon test was used for comparing the renal function of each period.

Results: The 6- and 12-month postoperative SRF values were decreased compared with the preoperative values. Multivariate analysis revealed that older age was related to a lower postoperative eGFR, and a longer warm ischemia time was related to a decreased postoperative SRF. Patients with a warm ischemia time of >30 minutes were correlated with a larger mean tumor size, higher “preoperative aspects and dimensions used for an anatomical” score, greater amount of blood loss during the operation, longer postoperative hospital stay, and lower postoperative SRF compared with patients with a warm ischemia time of <30 minutes. Patients in the RPN group had shorter warm ischemia time and higher 6-month postoperative SRF compared with patients in the LPN group.

Conclusion: SRF is more sensitive for postoperative follow-up than eGFR. Longer warm ischemia time is associated with poorer postoperative renal function. RPN is a safe and feasible alternative to LPN.

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Keywords: laparoscopy; nephrectomy; robotics; warm ischemia**1. Introduction**

Nephron-sparing surgery has gained popularity in the treatment of T1 renal tumors.¹ It provides a similar cancer control outcome to radical nephrectomy with the benefit of

renal function preservation.² The introduction of minimally invasive surgery has also become more acceptable because of improved cosmetic results and less pain after the operation; however, the steep learning curve and the difficulty of intracorporeal suturing have limited the widespread use of laparoscopic partial nephrectomy (LPN).³ The emergence of robot-assisted partial nephrectomy (RPN) has shown promising results and involves a shorter learning curve and decreased warm ischemia time (WIT), total operation time, and estimated blood loss (EBL) in some studies.^{1,4} The optimal length of WIT is debatable, with some investigators reporting that a cutoff of 20 minutes, 30 minutes, or 40

Conflicts of interest: The authors declare that there are no conflicts of interest related to the subject matter or materials discussed in this article.

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<http://dx.doi.org/10.1016/j.jcma.2014.09.002>

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minutes or longer causes a decline in renal function.^{5–7} Patel and Eggener⁸ coined the phrase “every minute matters” to stress the negative effect of longer WIT on renal function. We present the largest series of minimally invasive partial nephrectomy data in Taiwan and share our experience of postoperative outcomes in terms of overall, LPN, and RPN results.

2. Methods

From April 2004 to July 2012, a total of 94 patients received LPN and 75 patients underwent RPN in our institute. We obtained verbal informed consent from all patients and followed the provisions of the Declaration of Helsinki. Most (>90%) of the operations were performed by one surgeon. Patients with missing data, solitary kidney, intraoperative conversion to open nephrectomy, or bilateral renal surgery were excluded from this study. The estimated glomerular filtration rate (eGFR) and split renal function (SRF) were used as representatives of postoperative renal functions. The eGFR was calculated using the Modification of Diet in Renal Disease equation:

$$\text{eGFR} = 186 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times 0.742 (\text{in females}). \quad (1)$$

The SRF was calculated as the percentage of effective renal plasma flow (ERPF) of the diseased kidney divided by the total ERPF. ERPF is a nuclear medicine test. I-131-orthoiodohippurate (300 μCi) was injected for the test. The patient was instructed to lay supine on the examination table of the machine; then, the activity of the injected agent over the bilateral renal area was recorded for 27 minutes, and the emissions of both sides were counted and calculated. The emission over the bladder was also recorded for 1 hour for pre- and postvoiding activity. The total and each side's emission activity were then reported. The renal functions were monitored at three different time points: preoperatively, 6 months postoperatively, and 12 months postoperatively. We evaluated the correlation of renal function with age, body mass index, EBL, higher “preoperative aspects and dimensions used for an anatomical” (PADUA) score,⁹ and preoperative tumor size on a computed tomography scan with the aforementioned time points. Frozen sections were not routinely sent for pathological evaluation during the surgery; this was only done if the surgeon suspected that the surgical margin was not free of tumor.

In the second part of our study, the patients who had received minimally invasive partial nephrectomy were divided into two groups: WIT ≤ 30 minutes and WIT > 30 minutes. Change in renal function was evaluated at the previously mentioned time points. In the third part of the study, we divided minimally invasive partial nephrectomy patients into RPN and LPN groups and evaluated the correlation of postoperative renal function between the two groups.

Means and standard deviations were used for reporting continuous variables. The Mann–Whitney test was used to compare continuous variables, and Chi-square test was used

for comparing categorical variables, which were used to compare the perioperative parameters between the WIT ≤ 30 minutes and WIT > 30 minutes groups and also between the LPN and RPN groups. The Friedman test was used to evaluate the significance of change of renal functions 6 months and 12 months postoperatively compared with preoperative values, and the Wilcoxon test—modified using the Bonferroni correction method—was used for comparing the renal functions of each period. All tests were two-sided, and $p < 0.05$ was considered statistically significant, except with the Bonferroni correction method ($p < 0.0167$ revealed significance). All statistical analyses were performed using PASW Statistics version 18.0 (SPSS Inc., Chicago, IL, USA).

3. Results

There were 169 patients enrolled in the study. Two of those received surgery on both kidneys, and three underwent intraoperative conversion to radical nephrectomy owing to the intraoperative surgical margin frozen section being positive for malignant cells. There were 52 patients with incomplete preoperative and follow-up data, which left 102 patients in our study. Of the 102 patients, 64% were men and 46% received RPN. The mean overall age was 57.1 ± 13.7 years, the mean American Society of Anesthesiologists score was 2.03 ± 0.63 , and the mean tumor size was 3.75 ± 1.81 cm. The mean overall operative time was 256.9 ± 79.7 minutes, the mean WIT was 35.4 ± 21.7 minutes, and the mean EBL was 403.4 ± 607.3 mL. The median PADUA score was 8.1 ± 1.6 points, the percentage of malignant lesions was 56.9%, and the mean postoperative hospital stay was 6.0 ± 2.7 days (Table 1). The 6-month postoperative eGFR (81.43 ± 26.3) was decreased compared with the preoperative values (87.95 ± 24.46 , $p < 0.001$), but the 12-month postoperative eGFR (82.28 ± 25.04) did not reach statistical significance when comparing with preoperative and 6-month postoperative values ($p = 0.074$ and $p = 0.215$, respectively; Table 2). Both the 6- and 12-month postoperative SRF (0.42 ± 0.13 and 0.44 ± 0.07 , respectively) showed a significant decrease

Table 1
Patient characteristics.

Age (y)	57.1 ± 13.7
Sex: male/female (%)	65/37 (64/36)
No. of patients: RPN/LPN (%)	47/55 (46/54)
ASA score	2.03 ± 0.63
Mean tumor size (cm)	3.75 ± 1.81
Operative time (min)	256.9 ± 79.7
WIT (min)	35.4 ± 21.7
EBL (mL)	403.4 ± 607.3
PADUA score	8.1 ± 1.6
No. of malignant lesions (%)	68 (56.9)
Postoperative hospital stay (d)	6 ± 2.7

ASA = American Society of Anesthesiologists; EBL = estimated blood loss; LPN = laparoscopic partial nephrectomy; PADUA score = preoperative aspects and dimensions used for an anatomical classification score; RPN = robot-assisted partial nephrectomy; WIT = warm ischemia time.

Table 2
Postoperative renal function.

	Preoperatively	6 mo postoperatively	<i>p</i> *	12 mo postoperatively	<i>p</i> *
eGFR	87.95 ± 24.46	81.43 ± 26.30	<0.001 ^a	82.28 ± 25.04	0.074 ^b 0.215 ^c
SRF (diseased kidney)	0.49 ± 0.05	0.42 ± 0.13	<0.001 ^a	0.44 ± 0.07	<0.001 ^b 0.779 ^c

* Statistical significance: *p* < 0.0167.
eGFR = estimated glomerular filtration rate; SRF = split renal function.
^a Preoperatively versus 6 months postoperatively.
^b Preoperatively versus 12 months postoperatively.
^c Six months postoperatively versus 12 months postoperatively.

compared with preoperative SRF (0.49 ± 0.05, both *p* < 0.001). The values of 6- and 12-month postoperative SRF did not reveal differences (*p* = 0.799). Increased age was correlated with poorer eGFR 6 months postoperatively (both *p* < 0.001), and a longer WIT was associated with poorer eGFR 12 months postoperatively (*p* = 0.034). SRF was only correlated with WIT (both *p* < 0.001, Table 3); the longer the WIT, the worse the postoperative SRF.

When the patients were split into two groups by pathological report (malignancy or benign), 68 patients were grouped in malignancy and 47 patients were grouped in benign. The benign pathology group had SRFs of 0.48, 0.46, and 0.46 prior to the operation, 6 months after the operation, and 12 months after the operation, respectively, whereas the malignancy group had SRFs of 0.49, 0.44, and 0.44, respectively, at the aforementioned time points. The SRF did not show any significant difference at any of these three time points (*p* = 0.42, *p* = 0.11, and *p* = 0.19) between the two groups.

In the second part of the study, the patients were grouped by a WIT ≤30 and >30 minutes. The mean age and American Society of Anesthesiologists score of these two groups were similar, but the mean tumor size was 3.28 ± 1.83 cm in the WIT ≤30 minutes group and 4.21 ± 1.73 cm in the WIT >30 minutes group (*p* = 0.010). The EBL was 230.5 ± 226.1 mL versus 605.7 ± 819.9 mL (*p* = 0.004), the PADUA score of the tumor was 7.6 ± 1.4 versus 8.6 ± 1.6 (*p* = 0.001), and the postoperative hospital stay was 5.4 ± 2.2 days versus 6.7 ± 2.8 days (*p* = 0.013) in the WIT ≤30 minutes group and the WIT >30 minutes group. The eGFR value was significantly lower 6 months postoperatively if the WIT was >30 minutes

(86.3 ± 27.0 vs. 75.6 ± 24.5, *p* = 0.044), and SRF was significantly lower at both 6 months and 12 months postoperatively if the WIT was >30 minutes (0.48 ± 0.05 vs. 0.42 ± 0.06 at 6 months and 0.48 ± 0.04 vs. 0.41 ± 0.06 at 12 months, both *p* < 0.001).

The operation time and the WIT were longer in the LPN group compared with the RPN group [284.9 ± 83.3 minutes vs. 224.0 ± 61.3 minutes (*p* < 0.001) and 43.3 ± 23.5 minutes vs. 26.1 ± 14.9 minutes (*p* < 0.001), respectively; Table 4]. The eGFR between the two groups was similar, and SRF was lower in the LPN group at 6 months postoperatively compared with the RPN group (0.43 ± 0.06 vs. 0.47 ± 0.06, *p* = 0.001). In the LPN group, both the 6- and 12-month postoperative eGFR and SRF were significantly decreased compared with the preoperative values (Table 5). In the RPN group, only the 12-month postoperative SRF was lower than the preoperative value (Table 6).

4. Discussion

Nephron-sparing surgery has become the standard procedure for treating T1 renal tumors, even in patients with a normal contralateral kidney.¹⁰ The length of WIT has been reported as the most important predictor of postoperative renal function after minimally invasive partial nephrectomy, despite the clear cutoff value still being debatable.^{5–7,11} However, “every minute matters” was proposed by Patel and Eggener⁸ to emphasize that, the shorter the WIT, the higher the possibility of better postoperative renal function recovery.

In our series, the patients who received minimally invasive partial nephrectomy showed a decrease in eGFR 6 months

Table 3
Overall SRF of diseased kidney.

	6 mo postoperatively		12 mo postoperatively	
	Coefficient	<i>p</i>	Coefficient	<i>p</i>
Age (y)	0.000 (−0.001–0.000)	0.410	0.002 (0.000–0.001)	0.180
BMI	−0.001 (−0.004–0.002)	0.516	−0.001 (−0.004–0.002)	0.658
EBL	6.315E−6 (0.000–0.000)	0.552	6.554E−6 (0.000–0.000)	0.827
WIT	−0.002 (−0.004–−0.001)	<0.001	−0.002 (−0.002–0.001)	<0.001
Tumor size (cm)	0.000 (−0.001–0.001)	0.711	0.000 (−0.001–0.000)	0.228
PADUA	−0.002 (−0.010–0.006)	0.626	−0.015 (−0.038–0.008)	0.568

BMI = body mass index; EBL = estimated blood loss; PADUA score = preoperative aspects and dimensions used for an anatomical classification score; SRF = split renal function; WIT = warm ischemia time.

Table 4
 Perioperative data comparison between the LPN and RPN groups.

	LPN	RPN	<i>p</i>
Age (y)	58.7 ± 14.0	55.2 ± 13.2	0.199
Sex: male/female (%)	38/17 (69/31)	23/24 (49/51)	
ASA score	2.13 ± 0.64	1.94 ± 0.60	0.952
Mean tumor size (cm)	3.59 ± 1.72	3.85 ± 1.98	0.472
Operative time (min)	284.9 ± 83.3	224.0 ± 61.3	<0.001
WIT (min)	43.3 ± 23.5	26.1 ± 14.9	<0.001
PADUA score	8.2 ± 1.5	7.9 ± 1.7	0.288
EBL (mL)	472.5 ± 739.6	322.4 ± 394.1	0.196
Postoperative hospital stay (d)	6.3 ± 2.7	5.6 ± 2.3	0.167

ASA = American Society of Anesthesiologists; EBL = estimated blood loss; LPN = laparoscopic partial; PADUA score = preoperative aspects and dimensions used for an anatomical classification score; RPN = robot-assisted partial nephrectomy; WIT = warm ischemia time.

postoperatively and a decrease in SRF at 6 months and 12 months postoperatively compared with the preoperative values. There was no significant recovery of SRF from 6 months to 12 months postoperatively. This may indicate that renal function is affected by the surgery, and SRF may be more sensitive in evaluating the extent of damage. This finding coincides with that of Porpiglia et al,¹¹ who reported that serum creatinine level has low sensitivity in evaluating renal damage, and that the SRF remained stable on further follow-up.

In multivariate regression analysis for evaluating parameters that are related to the change of renal function, age was associated with a decrease in eGFR 6 months and 12 months postoperatively, and WIT was associated with a decrease in eGFR 6 months postoperatively. SRF was not associated with age and was solely associated with WIT. However, because age is one of the variables in the Modification of Diet in Renal

Disease equation, it is understandable that age is associated with a change in eGFR. When using eGFR to assess damage to one kidney, the real damage can be compensated for by increasing the function of the other kidney, thus masking the true damage caused by partial nephrectomy.¹² Therefore, SRF is more sensitive than eGFR in revealing postoperative renal function.¹² All of our patients underwent nuclear scintigraphy scanning for the evaluation of the percentage of diseased kidney to total renal function prior to and regularly after the operation, which is the strength of this study and truly revealed that the renal function of diseased kidneys actually decreased after the operation using this method.

A smaller tumor size, a lower PADUA score, a shorter hospital stay, and less blood loss were observed in patients with a WIT of <30 minutes. These findings were similar to those obtained in previous studies.^{10,13} Our series also observed that in patients with a WIT <30 minutes, the decline of eGFR did not show statistical significance, and only SRF revealed decreased diseased kidney function, which again revealed that SRF is more sensitive than eGFR in predicting individual kidney damage.

In our series, the RPN group had a shorter WIT compared with the LPN group. The postoperative eGFR was similar in both groups, and only the 6-month postoperative SRF was lower in the LPN group compared with the RPN group, indicating that RPN is a safe and feasible alternative to LPN.

One limitation of this study lies in our inability to calculate the volume of resected normal renal parenchyma, which may have influenced postoperative renal function. In addition, the follow-up period only lasted 1 year postoperatively; further follow-up of renal function is required, with a larger database.

Table 5
 Postoperative renal function in the LPN group.

	Preoperatively	6 mo postoperatively	<i>p</i> *	12 mo postoperatively	<i>p</i> *
eGFR	86.7 ± 22.3	78.6 ± 22.5	0 < 0.001 ^a	80.2 ± 23.4	0.006 ^b 0.176 ^c
SRF (diseased kidney)	0.49 ± 0.06	0.43 ± 0.06	<0.001 ^a	0.44 ± 0.06	<0.001 ^b 0.316 ^c

* Statistical significance: *p* < 0.0167.

eGFR = estimated glomerular filtration rate; LPN = laparoscopic partial nephrectomy; SRF = split renal function.

^a Preoperatively versus 6 months postoperatively.

^b Preoperatively versus 12 months postoperatively.

^c Six months postoperatively versus 12 months postoperatively.

Table 6
 Postoperative renal function in the RPN group.

	Preoperatively	6 mo postoperatively	<i>p</i> *	12 mo postoperatively	<i>p</i> *
eGFR	89.4 ± 25.9	84.6 ± 30.0	0.093 ^a	84.8 ± 27.1	0.726 ^b 0.688 ^c
SRF (diseased kidney)	0.49 ± 0.05	0.47 ± 0.06	0.030 ^a	0.46 ± 0.06	0.001 ^b 0.039 ^c

* Statistical significance: *p* < 0.0167.

eGFR = estimated glomerular filtration rate; RPN = robot-assisted partial nephrectomy; SRF = split renal function.

^a Preoperatively versus 6 months postoperatively.

^b Preoperatively versus 12 months postoperatively.

^c Six months postoperatively versus 12 months postoperatively.

In conclusion, this is the largest study of postoperative renal function change using eGFR and SRF in Taiwan. SRF was more sensitive for postoperative follow-up than eGFR as it examined the renal function of each kidney instead of the global function. An additional result is that RPN is a safe and feasible alternative to LPN because it had a shorter operation time and WIT, and better SRF at 6 months after the operation.

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